THE MAXWELL DEMON IN SHEEP'S CLOTHING*

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LIFE presents itself in many forms. To him who is engaged in pursuing the science of the human body, the first impression is that offered by a complex organism of many special parts, each performing distinct tasks and made to work in unison. This is not unlike the homeostasis, integration, feedback, and central control that go into the performance of an orchestra, although, and rather unlike a good orchestra, its adaptability is such that a great many instances of imperfection can be tolerated. Much can be learned, and is being learned, from the study of this complex subject as a whole, or of its major parts and subdivisions. Indeed the very complexity is leading to the formulation of principles that confer upon integrative physiology some viewpoints hardly anticipated a generation ago.

Besides integration, the other great group of physiological problems deals with the ultimate mechanisms which enable organs and cells to fulfill their functions, and here we come into contact with the most penetrating efforts to understand the details of those workings of nature which we have wondered about since the beginnings of philosophy and experimented on for a century or more. Thus, unless we remain content at wondering (which might have been the better part of wisdom, but it is too late to help that now), we seek to elucidate the mechanisms of the specific manifestations of each organ by means of the analytical, as opposed to the descriptive and the synthetic parts of our research. This is something of a compulsion, drawing us incessantly to find the next cause, the next building stone, the next more detailed principle of operation.

A number of years ago, I commenced an essay on molecular

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physiology with a passage from Guy de Pourtalès' "*La Pêche Miraculeuse*," which is fitting to repeat here: "How unfortunate," he said, "that we have not a long series of lives at our disposal, for we find universe within universe the further we explore, like those Japanese lacquer boxes that you buy in Port Said, the smallest of which is so tiny that you can't open it at all." This neatly describes the way of our analytical research, which, having found one mechanism, one cause, in one little box, is immediately forced to ask about its mechanism, its cause, doubtless hidden in the next smaller box. And the last, the smallest of them all, is surely thought to hide the ultimate mechanism, the key to all our mysteries.

We have already arrived in a world of very small and secret boxes, down to the size of single, large molecules. And still we have not yet understood everything, far from it. Some of us, driven further by our common compulsion, conclude that this is not yet the ultimate level, that there still must be an even smaller box, where "the secret of life" is hidden in the abstract realm of quantum mechanics; and one, behold, has even proved that self-reproducing life is quantum-mechanically impossible, a somewhat surprising climax to the *cogito, ergo sum* of an earlier and perhaps wiser philosopher. Others among us realize that the analytical mode of thought, powerful though it may be, has been applied under the constant if unrealized accompaniment of a progressive simplification. The approach seemed sound, anthropomorphously (or childishly) speaking. We see a little machine. How does it work? Perhaps there is a little man inside. So we open the machine, but do not find the little man. Perhaps he is inside the next smallest part. And so we look, and arrive at the smallest sensible dimensions, those of the molecules. And still no little man—when and where has he escaped? Well, he has gradually been whittled away, because at every step of further penetration we have, unconsciously, narrowed down the problem to what seemed to be its central essentiality, a procedure that has often been outstanding in the grandeur of its sweeping omissions. As long as we are aware of this, keep count of what we eliminate, and try to put things back together again, mentally or experimentally, there is nothing wrong with the analytical pursuit of biology, which in many areas is now in one of its most fruitful periods, if not always wholly conscious of its limitations. At any rate, it is a most satisfying pursuit, because the search for that little man is no

less fascinating than (and indeed quite akin to) similar searches for the magic stone or the fountain of youth. Let us, therefore, assume that our wisdom will take care of holistic synthesis, and look around at what goes on in the molecular realm of life, "the world of the neglected dimensions."

This is a strange world indeed, where we must look with a mental eye in addition to the electron microscope, a world populated with strange beings and bedfellows. Some of these have long been known, and occur in ancient mythologies. They live in the microcosm of our cells, ignorant of each other, as, in Philip Wylie's *The Disappearance*, two opposite human worlds coexist, each without notice of the other. Let us look at them in turn, as we might look into an imaginary heaven where we observe the saints and scriptural figures plying their customary trades, Job seated on the manure pile and Samson wrecking a building, while St. George spars with a dragon inside a small enclosure.

We might see the Phoenix, only we have to look carefully, because, unlike the one popularly depicted who lives 5 centuries and then sets fire to it all, the real one works all along and performs his combustion continuously. The constituents of the cell are not permanent, they decline and are rebuilt, and a constant stream of oxidation runs through life as a cool flame. Life burns itself and rises from its ashes, but it does so in a steady state, not cataclysmically as the ancients pretended for simplicity.

Close to the Phoenix labors Sisyphus. His work is really very similar, but he seems to be enjoying himself after the build-up he recently had from Albert Camus. See him rolling up his stone, sure it will come crashing down again. Like everything in this world, his stone is small, a few angstrom units only, and he must lift it through a membrane 100 or 200 angstroms thick. But there are so many stones, sodium, potassium, and they come through from both sides and must be kept separated. Why? Because the rules of this world demand that potassium be inside and sodium out. They fall back slowly enough for Sisyphus to replace them by the moderate effort of basal metabolism. But now and then an avalanche occurs (outside we call this excitation), and then there is a lot to be put back—it requires all of a refractory period.

Supervising all of this is the spirit of Laplace. He is everywhere at once and keeps track of every molecule, its speed and changes in direction. His computer stores, remembers, and predicts; he knows the

future and the past, and the past is the future. Time is an arrow for him as well, but it points in all directions and all directions are time. He knows all and decides all, but conceals himself in the invisible cloak of probability and indeterminism. He has no records and no notes, but he does leave instructions, written on strings but not in the code of the Incas. His strings are helical and built of groups of letters. They carry patterns for the future, for now there is a future, and time's arrow points. Some say they might also carry memory and thought, but that may be a mistake—nature still is guarding some secrets, even from the in-group. There are other strings, with nearly 26 letters. Do these bear messages too? We do not know. They are intricately folded and wound, some parts helical, some parts not. They form structures stranger than cathedrals, with a great architecture of growth and form, of function and control. They fold and twist (perhaps), and they form an allosteric engine of mechanisms stranger than man has devised.

Near these engines, our last little man is at work, a little demon in sheep's clothing. He seems to cheat the rules perhaps, sitting there on the lofty plane of Caratheodory, at the controls which let things happen in one direction and not another. Not really, though, because the laws here are inescapable; he merely uses the principles of anisotropy, and so does not cheat, as long as he invokes the principle of Curie. His chemodynamic engine is the true secret of life, at least it is to the analytical mind.

This brings me to the end of this little allegory. What is its sense?

It takes but little detailed knowledge of cell physiology to see the following general picture: whether it serves to perform external work or merely to reverse an internal dissipation, the molecular phenomenon of concern in the physiological aim to "accomplish something," energetically speaking, is the transformation of chemical energy into another, directed form. This is not so unusual; we ourselves have invented a number of engines and devices to do the same. All we must do is to make an arrangement that confers directionality to a chemical or thermal process, and this we can do in a steam or combustion engine or in an electric element. All such arrangements are subject to the limitations of the second law of thermodynamics. To break this law would mean to invoke a Maxwell demon, unadulterated, and we have good reason to think that this being does not exist. Our engines are

devices that make use of an energy flux or gradient, and merely see to it that the resulting transformation proceeds vectorially. They do so by macroscopic arrangements, the directional tendency of which is sometimes easy to see. There is no place in them for a Maxwell demon to hide. But in the living cell, the machinery is molecular, one engine molecule interacting with one molecule of a driving substance in a stoichiometric reaction. How can that be made vectorial and oriented? Is there no thermodynamic demon in sheep's clothing working at the level of these dimensions? Certainly not, the directing devices themselves are inherent in the engine molecules, where driving reactions and chemomechanical transductions will be seen to be one and the same thing once we understand them.

GLOSSARY OF ALLUSIONS

The "world of the neglected dimensions" is taken from the title of a book, *Die Welt der vernachlässigten Dimensionen,* by Wolfgang Ostwald, a lively account of the phenomena encountered in colloidal systems. The allegory of looking into an imaginary heaven is not original, but resembles a passage in a Dutch story, *Pieter Bas,* by Godfried Bomans. The allusion to cathedrals must be compared to the "cathedrals of thought" in the great work of Lewis and Randall* on thermodynamics. Caratheodory is harder to explain. This mathematician derived what is perhaps the most fundamental formulation of the second law of thermodynamics, based upon consideration of paths in a coordinate plane. Pierre Curie proposed a principle in his essay, *"Sur la symétrie dans les phénomènes physiques"* in which he pronounced that directional events must result from directional causes, or occur in an oriented medium. This is now formulated in irreversible thermodynamics as "Curie's theorem," in a vector analytical form which Curie might have difficulty in recognizing. The Maxwell demon, finally, is a well-known creature of a hypothetical nature. By opening a little slide or valve, he is supposed to let events arbitrarily happen in one direction and thus circumvent the second law. This essay notes that while devious or at least unknown mechanisms must be in use in biological energy transduction, no laws are violated.

*Lewis, G. N. and Randall, M. *Thermodynamics and the Free Energy of Chemical Substances.* New York, McGraw-Hill, 1923.